Preparation of 17β-(Hydroxymethyl)-3-methoxyestra-1,3,5(10)-trien-18-oic Acid 18,20-Lactone, a New *C(18)*-Oxygenated Steroid

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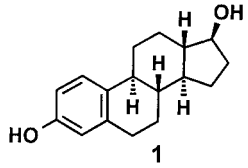
Lactone **13** was synthesized by intramolecular radical-mediated oxygenation of the angular Me(18) group of the 17β-configurated sterol **3**. Several substrate-controlled methods for stereoselective construction of the hydroxymethyl side chain of **3** were investigated.

Introduction. – Albeit 18-norsteroids appear quite similar to their naturally occurring counterparts – they differ only in the missing Me group – their synthesis has proven a rather difficult endeavour, and is in the case of 18-norestradiol (**1**) also somewhat ambiguous [1–3]. In our attempt for a new approach to the latter compound [4], we reinvestigated the various techniques to functionalize the angular Me(18) group in estradiol (**2**) itself and in its derivatives. Apart from the known *retro*-pinacol rearrangement[1]) and *Beckmann* fragmentation [6] of the corresponding 17-ketoxime, we examined an intramolecular radical-mediated oxygenation, the well-known *hypoiodite reaction* [7a]. To meet the configurative prerequisite that non-activated C-atoms in δ-position of alcohols are prone to attack by the *in situ* formed alkoxy radical [8], we had to introduce a β-configurated hydroxyalkyl side chain at C(17) in the case of **2**. Since no further additional chiral center at C(20) should be created, we anticipated the hydroxymethyl derivative **3** to be a conceivable precursor for the hypoiodite reaction[2]).



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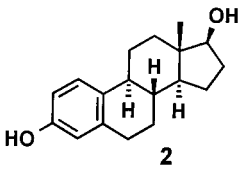

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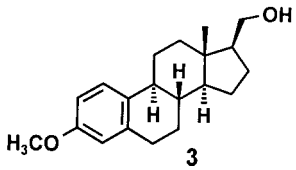

3

Results and Discussion. – Sterol **3** has previously been synthesized [9] in a total yield of 8 or 17%, respectively, starting from epoxide **4** which was easily obtained [10][11] (*Scheme 1*). However, this route suffers from the pyrolytic cleavage of **4**

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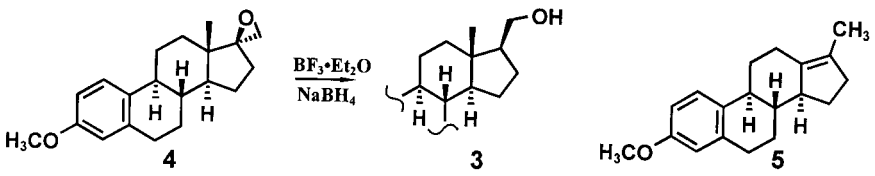
[1]) Alkene **5** is obtained from estradiol 3-methyl ether or the corresponding 17-(tosyloxy) derivative (see [1] and [5]). In accordance with the literature [1][5], the $\Delta^{13,14}$ isomer is also obtained in minor amounts (8%). Purification by TLC with $AgNO_3$-impregnated plates (22.5% $AgNO_3$, cyclohexane/AcOEt 19:1; R_f 0.60) provides pure **5** in 52 and 50% yield, respectively. Attempts to further functionalize the vinylic methyl group by treatment with SeO_2 lead to a complex mixture of oxygenation products, leaving, however, the vinylic methyl group untouched.

[2]) A hydroxymethyl group β-situated at C(17) instead of a substituted alkyl side chain has been demonstrated to have a yield-increasing effect in the pregnane series, due to missing steric hindrance [7b].

yielding mainly alkene **5**. Our preliminary attempts to prepare **3** from **4** by a *Lewis*-acid-catalyzed reductive ring opening [12] on treatment with $BF_3 \cdot Et_2O$ and $NaBH_3CN$ have led to alcohol **3** with high diastereoselectivity (α/β 5 : 95), but in only 46% yield.

Scheme 1



Therefore, two alternative routes have been developed (*Scheme 2*). The first one, which proceeds under complete diastereoselective control, starts from unsaturated nitrile **7** [13]. The latter is obtained by treatment of estrone methyl ether (**6**) with 2 equiv. of Me_3SiCN (TMSCN) [14] and subsequent dehydration with dry $Et_4NF/POCl_3$ in abs. pyridine. This one-pot procedure leads – after normal workup, followed by chromatography or *Soxhlet* extraction and crystallization – to pure **7** in 70% yield. The next four steps run very smoothly and in almost quantitative yield. Thus, saponification of **7** with NaOH in ethanol at elevated temperature (195°, sealed autoclave) and esterification of the resulting crude acid with Me_2SO_4 yields – after crystallization from MeOH – the previously unknown methyl ester **8**. Due to shielding by the Me(18) group, hydrogenation of **8** (3 bar, Pd/C in AcOEt/AcOH) occurs exclusively from the α-face, yielding pure 17β-configurated ester **9**, the physical properties of which are in accordance with the available literature data[3])[4]). Finally, reduction with $LiAlH_4$ in THF gave the pure alcohol **3**[5]) in 64% yield with respect to ketone **6**. The correct β-configuration at C(17) of **3** is checked by 2D NOESY NMR experiments (cross-peak between Me(18) (*s* at 0.67 ppm) and the two diastereotopic H–C(20) (2*dd* at 3.46–3.59 and 3.71–3.76 ppm)).

The second, even shorter, but in comparison with the above mentioned sequence lower-yielding route provides **3** *via* alkene **10** [16]. The latter is obtained from **6** on treatment with 4 equiv. of triphenylphosphonium methylid in 78% yield and then submitted to hydroboration and subsequent oxidative workup. The use of diborane in THF at 0° leads in our hands [9b] to a mixture of **3** and the undesirable 17α-diastereoisomer in a ratio of 3 : 1 (yield 62%), as indicated by ^{13}C-NMR spectroscopy[6]). Best results are achieved with 9-borabicyclo[3.3.1]nonane (9-BBN) at 0°, leading after oxidative workup and column chromatography to **3** and only traces of the

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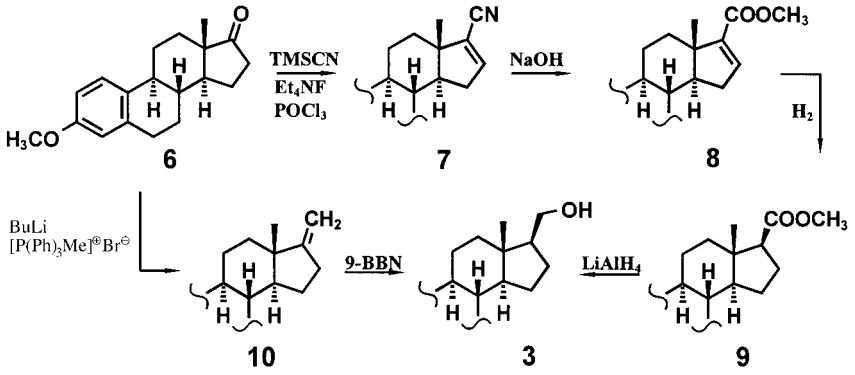
[3]) Hydrogenation of **7** is unfavourable since prolonged reaction times are needed. Furthermore, the saponification of the corresponding saturated nitrile leads to a 3 : 1 mixture, with preference for the 17β-diastereoisomer.

[4]) In the course of the structure elucidation of ouabagenine, a cardenolide from *Acokanthera schimperi*, etianic acid derivative **9** was prepared by hydrogenation of the corresponding Δ^{14} compound, a degradation product [15].

[5]) Our sample of **3** shows a m.p. identical with the one given in [9a], whereas its optical rotation agrees with [9b] (see *Exper. Part*).

[6]) Determined by integration of the ^{13}C-NMR signals of Me(18) of the 17β-isomer **3** and its 17α-isomer at 12.5 and 20.7 ppm, respectively.

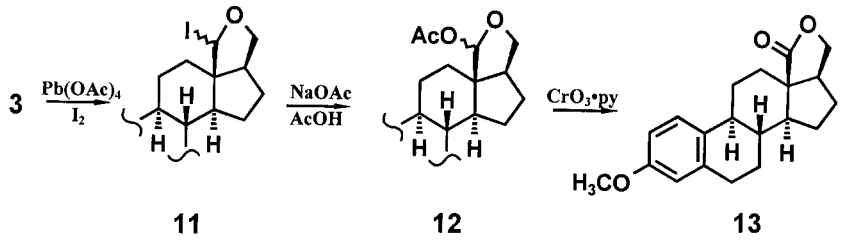
Scheme 2



corresponding epimer (α/β 5 : 95). The latter can be separated by a single crystallization from MeOH, yielding pure **3**[5]) in 46% with respect to **6**. It should be noted that these results do not differ from those achieved by direct application of *in situ* prepared 9-BBN. Since the latter is simply formed by reaction of inexpensive cycloocta-1,5-diene with $NaBH_4$ and $BF_3 \cdot Et_2O$, this method can be recommended as an economic alternative to the known procedure [17] utilizing neat 9-BBN.

The functionalization of the angular Me(18) group succeeds through a sequence of oxygenation steps (*Scheme 3*). Thus, a suspension of **3**, lead tetraacetate, powdered $CaCO_3$ (as a buffer), and iodine in cyclohexane is heated under reflux to give the primary products of the hypoiodite reaction [7a], the tetrahydro-2-iodofurans **11** which are not isolated. Instead the crude reaction mixture is heated in the presence of a solution of NaOAc in AcOH, providing the acylated hemiacetals **12**[7]) by displacement of the I-atom. These are directly oxidized [18] with $CrO_3 \cdot$ pyridine complex [19] to afford an oil (73%) from which pure lactone **13** precipitates after trituration with Et_2O.

Scheme 3



The structure of lactone **13** is unequivoqually assigned by ^{1}H-NMR spectroscopy and independantly established by X-ray diffraction (see *Fig.*) [20][8]); there is agreement with the spectroscopic data (see *Table* and *Exper. Part*).

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[7]) The ^{1}H-NMR spectrum of crude **12** shows the acetoxy groups at 2.05 (*s*) and 2.07 (*s*) ppm.

[8]) Observed torsion angles φ: H_{si}–C(20)–C(17)–H 88.7(5)°; H_{re}–C(20)–C(17)–H 32.5(5)°.

The oxymethylene group of the lactone moiety of **13** shows a significant set of ^{1}H-NMR signals. In contrast to the *dd* of the *re* located H–C(20) (4.35–4.38 ppm), only a *d* (4.12 ppm) is observed for the *si* facial H–C(20), which can be explained by means of a perpendicular orientation relative to the vicinal H–C(17) on application of the *Karplus* relation [21].

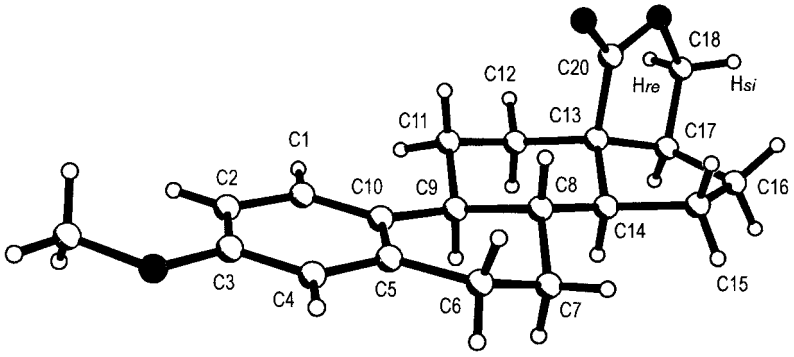

Figure. *Molecular structure of* **13**

Table. *^{13}C-NMR Chemical Shifts* [ppm] *of Compounds* **3**, **7**, **8**–**10**, *and* **13**

	3	**7**	**8**	**9**	**10**	**13**
C(1)	126.2	126.0	126.0	126.2	126.3	126.4
C(2)	111.3	111.4	111.4	111.5	111.4	111.4
C(3)	157.3	157.5	157.6	157.4	157.4	157.4
C(4)	113.7	113.8	113.8	113.7	113.7	113.7
C(5)	137.9	137.5	137.7	137.9	138.0	138.0
C(6)	29.8	29.4	29.6	29.8	29.4	29.7
C(7)	27.7	27.6	27.6	27.7	27.6	28.0
C(8)	38.4	37.1	37.1	38.9	38.7	36.4
C(9)	43.9	44.0	44.2	43.7	44.0	43.2
C(10)	132.8	132.0	132.7	132.5	132.7	131.8
C(11)	26.4	26.1	26.4	26.5	26.6	27.2
C(12)	38.6	34.0	34.8	38.5	35.7	31.6
C(13)	42.1	48.4	46.1	44.4	44.3	53.4
C(14)	54.9	55.1	51.0	54.9	53.4	45.3
C(15)	24.2	32.6	31.7	23.6	23.9	25.7
C(16)	25.6	147.2	34.8	24.1	29.9	31.5
C(17)	53.0	127.5	146.8	51.2	161.7	54.4
C(18)	12.5	16.3	16.1	13.5	18.5	179.3
C(20)	64.4	115.8	165.4	174.5	100.8	72.3
*Me*O–C(3)	55.1	55.1	55.1	55.2	55.1	55.1
*Me*O–C(20)	–	–	55.7	55.3	–	–

Experimental Part

General. All reagents and solvents are commercially available and used without further purification. Abs. CH_2Cl_2 is freshly distilled from 4-Å molecular sieve. Usual workup includes the washing of the org. layer with a sat. $NaHCO_3$ soln. and brine, followed by drying (Na_2SO_4 or $MgSO_4$), evaporation, and drying *in vacuo*. TLC: *Merck* silica gel *60 F_{254}* plates (Art. No. 5554); detection by UV, I_2, and phosphomolybdic acid. Column chromatography (CC): columns of different size filled with silica gel *60* (230–400 mesh) from *Merck Co*. M.p.'s: instrument model *571* by *Büchi Co*; not corrected. Optical rotations: *Perkin-Elmer-141* automatic polarimeter (10-cm, 1-ml cell); at r.t. IR Spectra: *Nicolet-Impact-400* instrument; films or KBr discs in cm^{-1}. NMR Spectra: *Bruker DRX 400* (^{1}H, 400.13 MHz; ^{13}C 100.61 MHz); δ in ppm downfield from internal Me_4Si (= 0 ppm) and

$CDCl_3$ (77.0 ppm), *J* in Hz. MS: *MAT 8230* by *Finnigan Co.* (EI 70 eV); *m/z* (rel. intensities in %). The elemental analyses were carried out on a *Leco-CHNS-932* instrument.

3-Methoxyestra-1,3,5(10),16-tetraene-17-carbonitrile (**7**). A soln. of **6** (1.42 g, 5.0 mmol) in abs. CH_2Cl_2 (20 ml) is treated with Me_3SiCN (0.99 g) and ZnI_2 (0.05 g) for 72 h under reflux. Evaporation yields the 17β-protected cyanohydrine as a single diastereoisomer which is dissolved in abs. pyridine (6 ml) and added dropwise at r.t. within 20 min to a soln. of Et_4NF (1.19 g, 8.0 mmol) and $POCl_3$ (6.1 g, 40 mmol) in abs. pyridine (11 ml). After stirring for 60 min at r.t. and 90 min under reflux, the cooled soln. is poured onto ice (100 g). Acidification with conc. HCl soln., separation of the precipitate, and usual workup yields crude **7** which is purified by *Soxhlet* extraction Et_2O (425 ml) CH_2Cl_2 (25 ml) and crystallization from Et_2O (20 ml) or CC (cyclohexane/AcOEt 4:1; R_f 0.47): 1.04 g (70%) of **7**. M.p. 166–168°. $[\alpha]_D^{20} = +68$ ($c = 1.00$, $CHCl_3$). IR (KBr): 2210 (CN). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.94 (*s*, Me(18)); 2.88–2.92 (*m*, 2 H–C(6)); 3.77 (*s*, MeO); 6.64 (*d*, $^4J(2,4) = 2.5$, H–C(4)); 6.65–6.66 (*dd*, $^3J(16,15) = 1.9$, $^3J(16,15) = 3.0$, H–C(16)); 6.70–6.73 (*dd*, $^3J(2,1) = 8.5$, $^4J(2,4) = 2.6$, H–C(2)); 7.25 (*d*, $^3J(1,2) = 8.5$, H–C(1)). ^{13}C-NMR: *Table.* MS: 293 (100, $M^{+\cdot}$), 278(6), 186(12), 173(17), 160(67), 43(95). Anal. calc. for $C_{20}H_{23}NO$: C 81.87, H 7.90, N 4.77; found: C 81.30, H 8.20, N 4.75.

Methyl 3-Methoxyestra-1,3,5(10),16-tetraene-17-carboxylate (**8**). In a sealed autoclave (200 ml), **7** (0.59 g, 2.0 mmol) and a soln. of NaOH (2.0 g, 50 mmol) in H_2O (10 ml) are heated for 9 h at 195°. Evaporation and acidification with conc. HCl soln. (8.0 ml) yield after filtration, the crude acid, which is treated with Me_2SO_4 (0.39 ml) and K_2CO_3 (0.69 g) abs. acetone (75 ml) under reflux for 24 h. The ester obtained after usual workup is purified by crystallization from MeOH (40 ml): 0.61 g (95%) of **8**. M.p. 136–138°. $[\alpha]_D^{20} = +82$ ($c = 1.00$, $CHCl_3$). IR (KBr): 1709 (CO). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*s*, Me(18)); 2.85–2.92 (*m*, 2 H–C(6)); 3.74 (*s*, COOMe); 3.77 (*s*, MeO); 6.63 (*d*, $^4J(2,4) = 2.7$, H–C(4)); 6.70–6.72 (*dd*, $^3J = 8.6$, $^4J(2,4) = 2.7$, H–C(2)); 6.79–6.81 (*dd*, $^3J(16,15) = 1.8$, $^3J(16,15) = 3.3$, H–C(16)); 7.20 (*d*, $^3J(1,2) = 8.6$, H–C(1)). ^{13}C-NMR: *Table.* MS: 326 (100, $M^{+\cdot}$), 311(11), 295(10), 267(10), 198(21), 173(19). Anal. calc. for $C_{21}H_{26}O_3$: C 77.27, H 8.03; found: C 77.60, H 8.20.

Methyl 3-Methoxyestra-1,3,5(10)-triene-17-carboxylate (**9**). A soln. of **8** (0.494 g, 1.50 mmol) in AcOEt (150 ml) and AcOH (0.3 ml) is shaken for 28 h with 10% Pd/C (0.1 g) under 3 bar H_2 pressure. Usual workup gives pure **9** (0.483 g, 98%). M.p. 165–166°. $[\alpha]_D^{20} = +97$ ($c = 1.00$, $CHCl_3$). IR (KBr): 1730 (CO). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.69 (*s*, Me(18)); 2.44 (*t*, $^3J(17,16) = 9.1$, H–C(17)); 2.84–2.86 (*m*, 2 H–C(6)); 3.69 (*s*, COOMe); 3.77 (*s*, MeO); 6.62 (*d*, $^4J(2,4) = 2.6$, H–C(4)); 6.69–6.72 (*dd*, $^3J(2,1) = 8.6$, $^4J(2,4) = 2.6$, H–C(2)); 7.20 (*d*, $^3J(1,2) = 8.6$, H–C(1)). ^{13}C-NMR: *Table.* MS: 328 (100, $M^{+\cdot}$), 297(6), 269(4), 227(16), 199(51), 173(44). Anal. calc. for $C_{21}H_{28}O_3$: C 76.79, H 8.59; found: C 76.10, H 8.85.

Methoxyestra-1,3,5(10)-triene-17β-methanol (**3**). a) *From* **9**. A soln. of **9** (0.443 g, 1.35 mmol) in abs. THF (25 ml) is added within 5 min to a suspension of $LiAlH_4$ (0.103 g, 2.7 mmol) in abs. THF (30 ml) at r.t. The mixture is stirred for 24 h 0°, then treated with H_2O (0.3 ml) and 5% NaOH soln. (0.6 ml) and stirred for 12 h at r.t. Then the mixture is dried (Na_2SO_4) and evaporated: pure **3** (0.398 g, 98%). M.p. 108–110° ([9a]: 108–109°; [9b]: 125°). $[\alpha]_D^{20} = +62$ ($c = 0.99$, $CHCl_3$) ([9a]: $[\alpha]_D^{20} = +23$ ($c = 0.50$, $CHCl_3$); [9b]: $[\alpha]_D^{20} = +64.5$). IR (KBr): 3450 (OH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.67 (*s*, Me(18)); 2.83–2.86 (*m*, 2 H–C(6)); 3.46 (*s*, OH); 3.46 (*dd*, $^2J(20,20') = 10.5$, $^3J(20,17) = 7.5$, H–C(20)); 3.71–3.76 (*dd*, $^2J(20,20') = 10.5$, $^3J(20,17) = 6.8$, H–C(20)); 3.76 (*s*, MeO); 6.62 (*d*, $^4J(2,4) = 2.7$, H–C(4)); 6.68–6.72 (*dd*, $^3J(2,1) = 8.6$, $^4J(2,4) = 2.7$, H–C(2)); 7.19 (*d*, $^3J(1,2) = 8.6$, H–C(1)). ^{13}C-NMR: *Table.* MS: 300 (100, $M^{+\cdot}$), 227(7), 199(26), 186(12), 173(31), 160(22). Anal. calc. for $C_{20}H_{28}O_2$: C 79.95, H 9.39; found: C 80.35, H 9.20.

b) *From* **10**. To a suspension of $NaBH_4$ (0.48 g) in abs. 1,2-dimethoxyethane (10 ml), THF (50 ml) and cycloocta-1,5-diene (1.73 g, 16.0 mmol) is added dropwise $BF_3 \cdot Et_2O$ (2.41 g). After 2 h stirring at 0° and 2 h under reflux, a soln. of **10** (2.26 g, 8.0 mmol) in abs. THF (25 ml) is added within 5 min at 0°. The mixture is stirred for 40 h at 0° and then treated with 30% H_2O soln. (8.0 ml) and 10% NaOH soln. (8.0 ml) for 4 h at 0°. Quenching with conc. NH_4Cl soln. (50 ml) followed by repeated extraction with Et_2O (450 ml; in total) gives, after usual workup, 4.0 g of an oil which is purified by CC (cyclohexane/AcOEt 1:1; R_f 0.53). Crystallization from MeOH (5.0 ml) yields pure **3** (1.41 g, 59%). This material is identical to that obtained above.

3-Methoxy-17-methylen-estra-1,3,5(10)-triene (**10**). A soln. of **6** (2.84 g, 10.0 mmol) abs. THF (250 ml) is added under reflux within 1 h to a soln. of the methylid prepared from methyltriphenylphosphonium bromide (14.3 g, 40 mmol) in abs. THF (150 ml) and 2.5M BuLi in hexane (18 ml, 45 mmol). After 7 h under reflux, the cooled mixture is treated with H_2O (100 ml) and evaporated. Acidification with dil. H_2SO_4 soln. and extraction with $CHCl_3$ (200 ml) yields, after usual workup crude **10**, which is purified by CC (cyclohexane/AcOEt 2:1; R_f 0.76) and crystallization from MeOH: **10** (2.19 g, 78%). M.p. 80–81°. $[\alpha]_D^{20} = +58$ ($c = 1.04$, $CHCl_3$). IR (KBr): 1653 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.81 (*s*, Me(18)); 2.84–2.89 (*m*, 2 H–C(6)); 3.76 (*s*, MeO);

4.67 (br. *s*, 2 H–C(20)); 6.63 (*d*, $^4J(2,4) = 2.5$, H–C(4)); 6.70–6.73 (*dd*, $^3J(2,1) = 8.7$, $^4J(2,4) = 2.5$, H–C(2)); 7.25 (*d*, $^3J(1,2) = 8.7$, H–C(1)). ^{13}C-NMR: *Table*. MS: 282 (100, $M^{+\cdot}$), 267(3), 239(3), 225(19), 186(23), 173(32). Anal. calc. for $C_{20}H_{26}O$: C 85.05, H 9.28; found: C 85.15, H 9.15.

17β-(Hydroxymethyl)-3-methoxyestra-1,3,5(10)-trien-18-oic Acid 18,20-Lactone (**13**). To a suspension of finely powdered $Pb(OAc)_4$ (3 g, 6.8 mmol) and $CaCO_3$ (1 g), obtained after 5 min stirring under reflux in cyclohexane (100 ml), I_2 (0.86 g, 3.4 mmol) is added in a single batch. After 1 h boiling, **3** (0.398 g, 1.32 mmol) is added neat to the hot suspension. Heating under reflux is continued for 4 h and then the slightly yellow suspension filtered hot. The filtrate is washed with sat. $Na_2S_2O_3$ soln. (2 × 10 ml) and evaporated. The obtained colourless oil is mixed with AcOH (12 ml), H_2O (3 ml) and NaOAc (1.5 g) and heated for 3 h under reflux. The cooled soln. is neutralized with $NaHCO_3$ soln. (100 ml) and extracted with Et_2O (3 × 50 ml). The solvent is evaporated and the residue dissolved at 0° in a soln. of CrO_3 (0.74 g) in H_2O/pyridine 1:1 (3 ml). After stirring for 24 h, the mixture is combined with an ice-cold soln. of $NaHSO_3$ (2 g) in H_2O (15 ml). Acidification with 1N HCl, followed by extraction with Et_2O (150 ml) yields, after usual workup, 0.30 g (73%) of impure **13**. An anal. sample (58 mg) is obtained by trituration with Et_2O (3.0 ml). M.p. 191–192°. $[\alpha]_D^{24} = +39$ (*c* = 1.00, $CHCl_3$). IR (KBr): 1750 (CO). ^{1}H-NMR (400 MHz, $CDCl_3$): 2.79–2.94 (*m*, 2 H–C(6)); 3.76 (*s*, MeO); 4.12 (*d*, ^2J(20*si*,20*re*) = 9.1, H_{si}–C(20)); 4.35–4.38 (1*dd*, ^2J(20*re*,20*si*) = 9.1, ^3J(20*re*,17) = 5.2, H_{re}–C(20)); 6.62 (*d*, $^4J(2,4) = 2.5$, H–C(4)); 6.68–6.71 (*dd*, $^3J(2,1) = 8.6$, $^4J(2,4) = 2.5$, H–C(2)); 7.19 (*d*, $^3J(1,2) = 8.6$, H–C(1)). ^{13}C-NMR: *Table*. MS: 312 (100, $M^{+\cdot}$), 298(8), 284(8), 253(4), 225(3), 199(8), 191(17). Anal. calc. for $C_{20}H_{24}O_3$: C 76.89, H 7.74; found: C 77.15, H 7.90.

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